PATENT COOPERATION TREATY

preliminary examination report
rapporteur's or client's
13-7-'05
termijn omzetten in reg./nat. fase:
PCT 2-6-'05

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VAN WESTENBRUGGE, Andries et al.
Nederlands Octrooibureau
Scheveningseweg 82,
P.O.Box 29720
NL-2502 LS THE HAGUE
PAYS-BAS

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	13.01.2005
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P045529PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL 03/00815	02.12.2003	02.12.2002

Applicant
ERASMUS UNIVERSITEIT ROTTERDAM et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Witzig, A Tel. +49 89 2399-5937

Form PCT/IPEA/416 (January 2004)

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045529PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/NL 03/00815	International filing date *(day/month/year)* 02.12.2003	Priority date *(day/month/year)* 02.12.2002
International Patent Classification (IPC) or national classification and IPC G01N21/65		
Applicant ERASMUS UNIVERSITEIT ROTTERDAM et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.06.2004	13.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mason, W Telephone No. +49 89 2399-2623

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL 03/00815

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-38 as originally filed

Claims, Numbers

1-36 received on 20.12.2004 with letter of 20.12.2004

Drawings, Sheets

1/8-8/8 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL 03/00815

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-36
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

RE SECTION VIII

Claim 25 should include a prior reference to "instrument" before "instrument further comprising" e.g. by insertion of "an instrument comprising" between the wording "providing" and "a laser".

RE SECTION V

1. The present application relates to an instrument comprising a laser, a fiber optic and a detection unit for detecting Raman scattered light, wherein the fiber has "substantially no Raman signal in one or more parts of the 2500-3700 cm-1 spectral region". The use of an instrument, a method for measurement using the instrument, and methods for evaluating an optical fiber using the instrument are also claimed. In medical applications the use of the Raman fingerprint region (400-2000 cm-1) has been used to obtain information on tissue samples. In this region however fibres which may be used for the medical probe generate strong background scattering in this region - the present application proposes the use of a fiber which "generates substantially no Raman signal in the region 2500-3700 cm-1" and detecting in this region.

   The following documents are referred to:

   D1=US5304173; D2=US2001012429; D3=US5652653; A1=EP0573535.

2. PRIOR ART

   D1 (Figs. 1-3) discloses methods and apparatus using optical fibers which are provided within a catheter and through which laser radiation is directed for the purpose of medical applications including diagnosis and removal of arterial or vascular obstructions (angiosurgery) and in particular diagnosis of atherosclerotic plaque, cancer and skin diagnosis. Reflection, elastic and inelastic scattering

including Raman scattering, absorption and fluorescence are used to diagnose tissue. The technique involves electronically sensing selected separated wavelengths of fluorescent or Raman scattered radiation returning from the material and generating an electronic signal representative of the selected separated wavelengths of fluorescent or Raman scattered radiation and electronically comparing the generated electronic signal with a stored reference signal such that the comparison results in a relationship allowing determination of the state of the tissue. In the preferred embodiment the core 22 and cladding 24 are fused silica and a protective buffer 26 is also provided.

D1 discloses that the instrument and method are used to determine the presence of atherosclerotic tissue - which tissue will therefore generate Raman signals in the range (2500-3700cm-1) which will be detected by the detection unit. D1 further discloses that the instrument and method are used for performing surgical procedures, in particular removal of biological tissue (biopsy).

D2 (Figs. 1-5) discloses method and apparatus for Raman spectroscopy using probes, for example in vivo / in vitro medical testing using a biomedical catheter. The probe is in the form of a fiber optic with a step-index, silica core/silica clad/polyimide buffer. Generally low OH- fibers are preferred - in some embodiments amorphous Teflon is used to create a cladding or coating, or a metal coating is used - both of which do not generate a signal in 2500-3700 cm-1 interval.

D3 (Fig. 2) discloses Raman spectrometry of sample to determine chemical compositions using a fiber optic comprising a fused silica core, doped fused silica cladding, and a polyamide buffer into which laser light from a krypton ion gas laser is launched.

A1 is similar teaching to D1 from the same inventors and discloses in addition the MEASUREMENT of the Raman spectrum (see Fig. 8), using quartz fused silica optical fibres in the fibre ATR Raman arrangement of Fig. 16, over the whole range 700 cm-1 to 4000 cm -1 identifying two peaks - one of which covers the range 2500 cm-1 to 3700 cm-1.

3. NOVELTY

In view of the above, independent claims 1, 11, 25 meet the requirement of novelty at least in view of the feature:

a): a signal analysis unit is used for analysing the Raman signal in the spectral region between 2500-3700 cm-1 according to an algorithm which outputs data regarding the molecular composition of the tissue and /or the clinical diagnostic class to which the tissue belongs.

4. INVENTIVE STEP

Re a):

As discussed above, A1 (Fig. 8) discloses that the detection unit is for MEASURING the Raman signal in the spectral region between 2500-3700 cm-1 (for the apparatus claims) and that the MEASURING of the Raman signal is in the spectral region between 2500-3700 cm-1 (for the method claims). However, A1 does not disclose or suggest that a signal analysis unit is used for ANALYSING the Raman signal in the spectral region between 2500-3700 cm-1 (for the apparatus claims) according to an algorithm which outputs data regarding the molecular composition of the tissue and /or the clinical diagnostic class to which the tissue belongs or similar steps for the method claims. In view of this feature independent claims 1, 11, 25 and dependent claims 2-10, 12-24, 26-36 therefore meet the requirement of inventive step since A1 (D1) although measuring (recording) such Raman signals with the detection unit does (do) not disclose that these Raman signals are analysed / used for analysis for the above purpose.

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New CLAIMS (20 December 2004)

1. Use of an instrument for measuring a Raman signal of tissue, the instrument comprising a laser, a signal detection unit for measuring the Raman signal, and a fiber optic probe, wherein the fiber optic probe comprises one or more optical fibers for directing laser light onto the tissue and for collecting light that is scattered by the tissue and guiding the collected light away from the tissue towards the signal detection unit, the fiber comprising a core, a cladding and optionally a coating, and the fiber or fibers for collecting light having substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, and wherein the detection unit records the Raman signal scattered by the tissue in said spectral region, wherein the fiber has substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the instrument further comprising a signal analysis unit which analyses the recorded Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the analysis comprising an algorithm which outputs data regarding the molecular composition of the tissue and/or the clinical diagnostic class to which the tissue belongs.

2. Use of an instrument according to claim 1, wherein the fiber optic probe comprises an optical fiber that both directs laser light onto the tissue and collects light that is scattered by the tissue and guides the collected light away from the tissue towards the signal detection unit.

3. Use of an instrument according to one of the preceding claims, wherein the fiber optic probe comprises at least one fiber having a low OH^- fused silica core.

4. Use of an instrument according to one of the preceding claims, wherein the fiber optic probe comprises at least one optical fiber having a fused silica core and a fused silica or Teflon or TECS cladding.

5. Use of an instrument according to one of the preceding claims, wherein the coating of the optical fiber comprises one or more of Teflon coatings and metal coatings.

6. Use of an instrument according to one of the preceding claims, wherein the detection unit substantially measures only the signal obtainable from the core of the optic fiber.

7. Use of an instrument according to one of the preceding claims, wherein Raman measurements can be combined with fluorescence and/or near-infrared absorption measurements and wherein the detection unit also comprises a detection unit for measuring the intensity and/or spectrum of tissue fluorescence and/or a detection unit for measuring near-infrared absorption.

8. Use of an instrument according to claim 7, wherein fluorescence and/or near-infrared absorption measurements make use of a fiber also used in obtaining Raman signal.

9. Use of an instrument according to one of the preceding claims, wherein the fiber optic probe is brought in, or in contact with, or in proximity to the tissue under investigation.

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10. Use of an instrument according to one of the preceding claims, wherein the tissue is excised, biopted or taken from a human or animal body before measuring.

11. An instrument for measuring a Raman signal of tissue, the instrument comprising a laser, a signal detection unit for measuring the Raman signal, and a fiber optic probe, wherein the fiber optic probe comprises one or more optical fibers for directing laser light onto the tissue and for collecting light that is scattered by the tissue and guiding the collected light away from the tissue towards the signal detection unit, the fiber comprising a core, a cladding and optionally a coating, and the fiber or fibers for collecting light having substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, and wherein the detection unit records the Raman signal scattered by the tissue in said spectral region, and wherein the fiber has substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the instrument further comprising a signal analysis unit which analyses the recorded Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the analysis comprising an algorithm which outputs data regarding the molecular composition of the tissue and/or the clinical diagnostic class to which the tissue belongs.

12. Instrument according to claim 11, wherein the fiber optic probe comprises an optical fiber that both directs laser light onto the tissue and collects light that is scattered by the tissue and guides the collected light away from the tissue towards the signal detection unit.

13. Instrument according to claim 11 or 12, wherein the fiber optic probe comprises at least one fiber.

14. Instrument according to one of claims 11-13, wherein the fiber optic probe comprises at least one optical fiber having a fused silica core and a fused silica or Teflon or TECS cladding.

15. Instrument according to one of claims 11-14, by using a coating material in which intrinsically little or substantially no signal is generated in the 2500-3700 cm^{-1} wavenumber interval.

16. Instrument according to one of claims 11-15, wherein the coating of the optical fiber comprises one or more of Teflon coatings and metal coatings.

17. Instrument according to one of claims 11-16, wherein the fiber comprises a first and a second coating, the first coating as coating on the cladding and the second coating as coating on the first coating, wherein the second coating comprises a laser light absorbing material.

18. Instrument according to one of claims 11-17, wherein the fiber comprises a first and a second coating, the first coating as coating on the cladding and the second coating as coating on the first coating, wherein the second coating comprises a material having a higher refractive index than the first coating material.

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19. Instrument according to one of claims 11-18, wherein the detection unit also comprises a detector for measuring fluorescence and/or a detector for near-infrared absorption.

20. Instrument according to one of claim 19 wherein fluorescence and/or near-infrared absorption measurements make use of a fiber also used in obtaining Raman signal and wherein the detection unit also comprises a detector for measuring fluorescence and/or a detector for near-infrared absorption.

21. Instrument according to one of claims 11-20 wherein the fiber optic probe comprises a bundle of fibers for measuring and/or scanning a tissue area.

22. Instrument according to one of claims 11-21, wherein the fiber optic probe comprises one optical fiber, the fiber having substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region.

23. Instrument according to one of claims 11-22, wherein the optical fiber comprises a laser light absorbing end tip coating.

24. Instrument according to one of claims 11-23, wherein the end face of the optical fiber, where the laser light is coupled into the optical fiber, is polished.

25. A method for producing and measuring a Raman signal of tissue, comprising providing a laser, a detection unit for measuring a Raman signal, and a fiber optic probe, wherein the fiber optic probe comprises one or more optical fibers for directing laser light onto the tissue and for collecting light that is scattered by the tissue and guiding the collected light away from the tissue toward the signal detection unit, the fiber comprising a core, a cladding and optionally a coating, sending laser light through the one or more optical fibers, receiving the Raman signal from the tissue through the one or more optical fibers and detecting the Raman signal by a signal detection unit, the fiber or fibers for collecting light having substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, and wherein the signal detection unit records the Raman signal in said spectral region, and wherein the fiber has substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the instrument further comprising a signal analysis unit which analyses the recorded Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region, the analysis comprising an algorithm which outputs data regarding the molecular composition of the tissue and/or the clinical diagnostic class to which the tissue belongs

26. Method according to claim 25, further comprising sending the laser light through a same optical fiber which also receives the Raman signal, using an optical fiber for this method which has substantially no Raman signal in one or more parts of the 2500-3700 cm^{-1} spectral region.

27. A method for measuring a Raman signal of a tissue sample, wherein an instrument according to one of claims 11-24 is used and wherein the tissue sample is excised, biopted or taken from a human or animal body before measuring.

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28. Method for evaluating an optical fiber for measuring a Raman signal of tissue, wherein an instrument according to one of claims 11-24 is used and wherein a tissue sample is excised, biopted or taken from a human or animal body before measuring, and wherein the Raman signal of the optical fiber is measured of the sample and of a blanc, and wherein the Raman signals of the sample and of the blanc are compared.

29. Method for evaluating the suitability of a type of fiber for measuring the Raman signal of tissue, comprising:
- using an instrument according to one of claims 11-24
- performing a measurement without tissue being present at the distal end of the fiber,
- performing a measurement with tissue being present at the distal end of the fiber,
- comparing the spectra obtained with and without tissue being present
- concluding that the fiber is suitable for measuring the Raman signal of tissue.

30. Instrument according to one claims 11-24, wherein part of the fiber is integrated or combined with a catheter that provides additional information about the tissue or which comprises means to obtain tissue samples, means to treat tissue and/or means used in surgical procedures.

31. Instrument according to one of claims 11-24, wherein the fiber optic probe comprises one single optical fiber.

32. Instrument according to one claims 11-24, wherein a mask over the fiber end face is applied, which only leaves the fiber core uncovered.

33. Instrument according to one of claims 11-24, wherein the coating of the optical fiber comprises an acrylate coating.

34. Use according to one of claims 1-10, for measuring a Raman signal of a tissue sample prior to it being resected, or biopted or for selecting tissue for biopsy or resection.

35. A method for measuring a Raman signal of a tissue sample, wherein an instrument according to one of claims 11-24 is used and wherein a Raman signal of a tissue sample is measured prior to it being resected or biopted.

36. A method for measuring a Raman signal of a tissue sample, wherein an instrument according to one of claims 11-24 is used and wherein a Raman signal of a tissue sample is measured for selecting this tissue for biopsy or resection.